

SELECTIVE COX-2 INHIBITION FROM PLANT EXTRACTSField of the Invention

The current invention is generally directed toward nutraceuticals that are nonsteroidal anti-inflammatory agents capable of inhibiting cyclooxygenase-2 (COX-2). The present invention relates to a method for inhibition of COX-2, or selective inhibition of COX-2 in an organism by administering to the organism organic extracts isolated from plants wherein such extracts inhibit COX-2 activity. The present invention also relates to purified compositions of the plant organic extracts. In addition, the current invention is directed toward a method for treating and/or preventing COX-2 mediated inflammation or inflammation-associated disorders in an organism.

Background of the Invention

The prostaglandins are a potent class of biologically active lipid derivatives that play a crucial role in the inflammatory response. The inflammatory response is a localized tissue response to injury or other trauma characterized by pain, heat, redness and swelling. Prostaglandins mediate this response by inhibiting platelet aggregation, increasing vascular permeability, increasing vascular dilation, inducing smooth-muscle contraction and causing the induction of neutrophil chemotaxis. Because of their central role in mediating the inflammatory response, significant efforts have been directed toward elucidating compositions that are capable of inhibiting the biosynthesis of prostaglandins.

Toward that end, prostaglandin biosynthesis has been extensively characterized. Prostaglandins are a group of oxygenated fatty acids that are generally derived from arachidonic acid. The biosynthesis of prostaglandins from arachidonic acid occurs in a three step process that includes 1) hydrolysis of arachidonic acid from phospholipid precursors catalyzed by a phospholipase A₂; 2)

cyclooxygenase ("COX") catalyzed oxygenation of arachidonic acid to prostaglandin G2 ("PGG2"). This COX catalyzed reaction is the first committed and rate limiting step in prostaglandin synthesis; and 3) conversion of prostaglandin G2 to the biologically active end product, prostaglandin, catalyzed by a series of synthases and reductases. Upon their synthesis, prostaglandins exit the cell and act in a hormone-like manner by effecting the target cell via G protein linked membrane receptors.

10 Inactivation of the COX enzyme is a natural target as a means to inhibit prostaglandin production due to this enzyme's pivotal role in the prostaglandin biosynthetic pathway. It is now known that two gene products possessing COX enzyme activity are expressed, termed COX-1 and COX-2.
15 COX-1 was the first discovered isoform and is constitutively expressed in most tissue types. Because it is constitutively expressed, COX-1 is available to participate in activities requiring a rapid physiological response and causes the production of prostaglandins involved in "house-keeping" functions. For example, COX-1 is responsible for acute production of prostaglandins that regulate vascular homeostasis, maintain gastrointestinal integrity, and maintain kidney function. Thus, COX-1 activity is responsible for the synthesis of prostaglandins required for
20 the maintenance of several cell types.

COX-2, on the other hand, is a recently discovered isoform that is inducibly expressed in response to numerous stimuli such as bacterial lipopolysaccharides, growth factors, cytokines, and phorbol esters. In addition, COX-2
30 is only expressed in a limited number of cell types including monocytes, macrophages, neutrophils, fibroblasts and endothelial cells. COX-2 expression, but not COX-1 expression, has been shown to increase in rheumatoid synovial tissue. Contrastingly, COX-2 expression is
35 inhibited in response to glucocorticoids and by anti-inflammatory cytokines. Thus, based upon these observations, COX-2 has been shown to be the isoform

responsible for mediating the production of prostaglandins that participate in the inflammatory response and inflammatory related disorders. In addition, COX-2 has also been shown to participate in certain cancers,
5 Alzheimer's disease, atherosclerosis, and central nervous system damage resulting from stroke, ischemia and trauma.

Corticosteroids provide one means to reduce effects associated with the inflammatory response. These potent anti-inflammatory agents exert their effect by causing a
10 reduction in the number and activity of immune system cells via various mechanisms. However, prolonged administration of corticosteroids results in drastic side effects that limit the therapeutic value of this class of anti-inflammatory agent.

15 Nonsteroidal anti-inflammatory drugs (NSAIDs) are also utilized as a means to reduce effects associated with the inflammatory response. The principal pharmaceutical effects of NSAIDs are due to their ability to prevent COX activity resulting in the inhibition of prostaglandin
20 synthesis. Inhibition of prostaglandin synthesis by NSAIDs is anti-pyretic, analgesic, anti-inflammatory, and anti-thrombogenic. However, administration of NSAIDs may also result in severe side effects such as gastrointestinal bleeding, ulcers and incidence of renal problems. NSAIDs
25 also inhibit both COX isoforms to varying degrees. For example, the most common NSAID, aspirin (acetylated derivative of salicylic acid), inhibits prostaglandin biosynthesis by irreversibly inactivating both COX-1 and COX-2 via acetylation of a serine residue located in the
30 arachidonic binding domain. While aspirin inactivates both isoforms, it is 10 to 100 times more effective inactivating COX-1 as opposed to COX-2.

The selective inhibition of COX-2 has been shown to be anti-inflammatory and analgesic without the associated
35 gastric and kidney related toxicity problems. This phenomenon is due to the discovery of NSAIDs that are capable of inhibiting COX-2, which is responsible for the

production of prostaglandins that mediate the inflammatory response, without causing the inhibition of COX-1, which is responsible for the production of prostaglandins that maintain both gastrointestinal integrity, and kidney
5 function. Thus, the beneficial effects of NSAIDs are separable from their drastic side effects by the development of COX-2 selective inhibitors.

Toward that end, several drugs that are COX-2 selective inhibitors of prostaglandin synthesis have been developed.
10 The most extensively characterized class of COX-2 selective inhibitor is diarylheterocycles, which include the recently approved drugs celecoxib and rofecoxib. However, other classes include, but are not limited to, acidic sulfonamides, indomethacin analogs, zomepirac analogs,
15 chromene analogs and di-t-butylphenols. For example, U.S. Pat. No. 5,380,738 describes oxazoles which selectively inhibit COX-2, U.S. Pat. No. 5,344,991 describes cyclopentenones which selectively inhibit COX-2, U.S. Pat. No. 5,393,790 describes spiro compounds which selectively
20 inhibit COX-2, WO94/15932 describes thiophene and furan derivatives which selectively inhibit COX-2, and WO95/15316 describes pyrazolyl sulfonamide derivatives which selectively inhibit COX-2.

In order to afford an alternative to drug-based
25 selective COX-2 therapy, it would be highly beneficial to provide nutraceuticals that inhibit COX-2, or even more preferably that selectively inhibit COX-2. A nutraceutical, in this context, is a composition that is a naturally occurring product that can safely be consumed and that
30 exhibits COX-2 inhibitory activity. In particular, it would be highly beneficial to obtain the nutraceutical composition or extract from a plant source due to the ability to derive a large quantity of the nutraceutical from a plant at a relatively affordable cost. These nutraceutical
35 compositions could be utilized in the diet in a preventative manner to maintain a "healthy" physiological state. The nutraceutical compositions could also be used as a means to

treat, cure or mitigate an existing inflammatory-related ailment either alone or in combination with another compound as a part of combination therapy.

Summary of the Invention

5 Among the several aspects of the invention therefore, is provided a method for inhibiting the activity of COX-2 in an organism, the method comprising the step of administering to the organism a therapeutically or prophylactically effective amount of an organic extract of a plant, wherein
10 the plant is selected from the order consisting of Agavales, Apocynales, Arales, Asterales, Basidiomycetae, Brassicales, Caryophyllales, Cycadales, Ebenales, Euphorbiales, Fagales, Hydrocharitales, Lamiales, Liliales, Loasales, Malvales, Myrtales, Palmales, Pandanales, Papaverales, Piperales,
15 Polemoniales, Polygalales, Primulales, Ranales, Rhamnales, Rosales, Rubiales, Rutales, Santalales, Sapindales, Scrophulariales, Umbellales, Urticales, and Violales.

Another aspect of the invention is a method for inhibiting the activity of COX-2 in an organism, the method
20 comprising the step of administering to the organism a therapeutically or prophylactically effective amount of an organic extract of a plant, wherein the plant is selected from the order consisting of Agavales, Apocynales, Arales, Asterales, Basidiomycetae, Brassicales, Caryophyllales,
25 Cycadales, Ebenales, Euphorbiales, Fagales, Hydrocharitales, Lamiales, Liliales, Loasales, Malvales, Myrtales, Palmales, Pandanales, Papaverales, Piperales, Polemoniales, Polygalales, Primulales, Ranales, Rhamnales, Rosales, Rubiales, Rutales, Santalales, Sapindales, Scrophulariales,
30 Umbellales, Urticales, and Violales, wherein the organic extract is a purified composition obtained by a method comprising contacting the plant with an organic solvent to remove an extract from the plant wherein the extract inhibits COX-2 activity and then isolating the extract with
35 COX-2 inhibitory activity.

Still another aspect provides a method of treating or preventing COX-2 mediated inflammation or an inflammation-associated disorder in an organism, the method comprising administering to the organism a therapeutically or
5 prophylactically effective amount of the purified composition of an organic plant extract wherein the purified composition is obtained by a method comprising contacting the plant with an organic solvent to remove an extract from the plant wherein the extract inhibits COX-2 activity and
10 then isolating the extract with COX-2 inhibitory activity.

Other features of the present invention will be in part apparent to those skilled in the art and in part pointed out in the detailed description provided below.

Brief Description of the Drawings

15 **Figure 1** depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Trichilia hirta*.

Figure 2 depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Capsicum frutescens*.

20 **Figure 3** depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Tradescantia virginiana*.

Figure 4 depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Tephrosia purpurea*.

Figure 5 depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Dracontomelon mangiferum*.

25 **Figure 6** depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Erythrina rubrinervia*.

Figure 7 depicts COX-2 > COX-1 inhibition by a plant extract isolated from *Pisonia aculeata*.

Abbreviations and Definitions

30 To facilitate understanding of the invention, a number of terms and abbreviations as used herein are defined below:

"Purified" means partially purified and/or completely purified. Thus, a "purified composition" may be either partially purified or completely purified.

"Extract" means crude extract, purified extract, and purified composition obtained by purification of the extract.

"COX activity" means the ability of either COX isoform, COX-1 or COX-2, to catalyze the oxygenation reaction of arachidonic acid to PGG2.

"COX inhibitor or COX inhibition" means a composition, agent or extract, purified or otherwise, that prevents either COX isoform, COX-1 or COX-2, from catalyzing the oxygenation reaction of arachidonic acid to PGG2 either in whole or in part.

"Selective inhibition of COX-2" means a composition, agent, or extract, purified or otherwise, which selectively inhibits COX-2 activity over COX-1 activity as determined by the ratio of the percentage of COX-2 inhibition divided by the percentage of COX-1 inhibition, unless otherwise indicated herein.

"IC₅₀" means the concentration (in mol L⁻¹) that reduces a specified response to 50% of its former value. As used herein this value measures the amount of composition, agent or extract (ug extract/ml solvent) causing 50% inhibition of PGE2 production. The IC₅₀ value may be used to determine COX-2 selectivity as specifically set-forth herein.

"Plant or parts thereof" means either the whole plant, or any part of the plant such as an aerial part, fruit, leaf, stem, or root and any combination thereof.

"Order", as utilized herein, is a taxonomic category of related organisms with a category consisting of a number of similar families.

"Family", as utilized herein, is a taxonomic category of related organisms ranking below the order and above the genus.

"Species", as utilized herein, is a fundamental taxonomic category ranking below a genus and consisting of a group of closely related individuals.

COX = the enzyme cyclooxygenase

COX-1 = the isoform cyclooxygenase-1

COX-2 = the isoform cyclooxygenase-2

NSAIDs = nonsteroidal anti-inflammatory drugs

PGE2 = prostaglandin E2

Description of the Preferred Embodiment

5 Applicants have discovered that organic extracts of certain plants or parts therefrom inhibit COX-2 activity. Applicants have also discovered that organic extracts of certain plants or parts therefrom selectively inhibit COX-2 activity. The inhibitory effect is selective because
10 inhibition of COX-2 is greater than inhibition of COX-1. Consequently, organic extracts of such plants or parts therefrom may be used to selectively inhibit the activity of COX-2 in an organism without causing an equivalent inhibition of COX-1 activity. Advantageously, these organic
15 extracts are nutraceuticals that may be safely consumed and provide an alternative to traditional drug-based therapy for COX-2 inhibition.

Accordingly, the extracts of the present invention preferably inhibit COX-2 activity more than COX-1 activity.
20 Preferably, the inhibitory effect of the plant extract on COX-2 is at least about two times greater than its inhibitory effect on COX-1. More preferably, the inhibitory effect on COX-2 is at least about 10 times greater than the inhibitory effect on COX-1. COX enzyme inhibition and
25 selectivity may be determined in accordance with any method generally known to those of ordinary skill in the field, as set forth in more detail below.

In addition to inhibiting COX-2, the organic extracts of the present invention may be isolated from an edible or
30 non-edible plant. In general, plants are classified as non-edible if they are utilized for a purpose other than nourishment and categorized as edible if they are consumed for the purpose of nourishment. For example, medicinal plants are considered non-edible because they are consumed
35 for the purpose of correcting symptoms of illness and are considered too potent to be consumed on a daily basis.

Classification of plants as edible versus non-edible, therefore, may be accomplished utilizing references commonly known to those skilled in the art for example, such references include, NAPRALERT; Tyozaburo Tanaka, (Edited by
5 Sasuke Nakoa) Tanaka's Cyclopedia of Edible Plants of the World, Keigaku Publishing Co., Tokyo, Japan, 1976; Stephen Facciola, Cornucopia II: A Source Book of Edible Plants, Kampong Publications, Vista, California, 1998; James A. Duke, Database of Phytochemical constituents of GRAS Herbs
10 and Other Economic Plants, CRC Press, Boca Raton, Florida, 1992; and George Macdonald Hocking, Dictionary of Natural Products, Plexus Publishing, Inc., Medford, New Jersey, 1997. The contents of these references are hereby incorporated in their entirety.

15 In a particularly preferred embodiment, organic extracts are isolated from plants of the following plant orders: Agavales, Apocynales, Arales, Asterales, Basidiomycetae, Brassicales, Caryophyllales, Cycadales, Ebenales, Euphorbiales, Fagales, Hydrocharitales, Lamiales,
20 Liliales, Loasales, Malvales, Myrtales, Palmales, Pandanales, Papaverales, Piperales, Polemoniales, Polygalales, Primulales, Ranales, Rhamnales, Rosales, Rubiales, Rutales, Santalales, Sapindales, Scrophulariales, Umbellales, Urticales, and Violales. The ability of
25 extracts isolated from plants of these particular orders to inhibit COX-2, selectively inhibit COX-2 and their use is set-forth below in **Tables 1-2**.

In order to prepare the extracts of the invention, a plant or parts thereof are ground into a fine powder, the
30 resultant powder is extracted with a solvent, and the extraction solvent is removed from the extract. The whole plant may be used or parts of the plant including an aerial part, fruit, leaf, stem, or root and any combination thereof may be used. If desired, the resultant extract may be
35 further purified to yield a purified extract or one or more purified compositions. The grinding step may be accomplished by any commonly known method for grinding a

plant substance. For example, the plant or parts thereof may be passed through a grinder to obtain a fine powder.

After the plant or parts thereof have been ground into a fine powder, they are combined with an extraction solvent.

5 The solution is then stirred at a temperature, and for a period of time, that is effective to obtain an extract with the desired inhibitory effects on the activity of COX-2. The solution is preferably not overheated, as this may result in degradation and/or denaturation of proteins in the
10 extract. The solution may be stirred at a temperature between about room temperature (25° C) and the boiling point of the extraction solvent. Preferably, the solution is stirred at about room temperature.

The length of time during which the plant powder is
15 exposed to the extraction solvent is not critical. Up to a point, the longer the plant powder is exposed to the extraction solvent, the greater is the amount of extract that may be recovered. Preferably, the solution is stirred for at least 1 minute, more preferably for at least 15
20 minutes, and most preferably for at least 60 minutes.

The extraction process of the present invention is desirably carried out using an organic solvent or a mixture of organic solvents. Organic solvents which may be used in the extraction process of the present invention, include but
25 are not limited to hydrocarbon solvents, ether solvents, chlorinated solvents, acetone, ethyl acetate, butanol, ethanol, methanol, isopropyl alcohol and mixtures thereof. Hydrocarbon solvents which may be used in the present invention include heptane, hexane and pentane. Ether
30 solvents which may be used in the present invention include diethyl ether. Chlorinated solvents which may be used in the present invention include dichloromethane and chloroform. Preferably, the solvent utilized for such extraction is a nonpolar organic solvent, such as
35 dichloromethane or hexane.

The relative amount of solvent used in the extraction process may vary considerably, depending upon the particular

solvent employed. Typically, for each 100 grams of plant powder to be extracted, about 500 ml of extraction solvent would be used. The organic solvent may be removed from the extract by any method known in the field of chemistry for removing organic solvents from a desired product, including, for example, rotary evaporation.

It is believed that the inhibitory effect of the plant extract of this invention on the activity of COX-2 is due to the presence of one or more compounds in the extract.

Compounds present in the extract which inhibit the activity of COX-2 may be isolated and purified by those of ordinary skill in the art employing methods known in the art. For example, column chromatography and fractional distillation may be used to obtain pure compounds from the plant extract of this invention.

The isolation and purification of particular compounds from the organic plant extracts of this invention may be performed as described in Resch, et al., J. Nat. Prod., 61, 347-350 (1998), the entire contents of which are incorporated by reference herein. The methods disclosed therein may be used to isolate and purify compositions which inhibit COX-2.

The ability of a particular organic extract to inhibit COX-1 or COX-2 is preferably determined by performing COX activity assays utilizing recombinant COX-1 and COX-2. The COX-1 and COX-2 genes may be subcloned from a variety of organisms, however in a preferred embodiment such genes are isolated from human or murine sources, using a variety of procedures known to those skilled in the art and detailed in, for example, Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, (1989) and Ausabel et al., Short Protocols in Molecular Biology, 3rd. ed., John Wiley & Sons (1995). Additionally, the subcloned portion of the particular COX gene may be inserted into a vector by a variety of methods. In a preferred method, the sequence is inserted into an appropriate restriction endonuclease site(s) in a

baculovirus transfer vector pVL1393 utilizing procedures known to those skilled in the art and detailed in, for example, Sambrook et al., *Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, 5 (1989) and Ausubel et al., *Short Protocols in Molecular Biology*, 3rd ed., John Wiley & Sons (1995).

The recombinant baculoviruses may be isolated by transfecting an appropriate amount of baculovirus transfer vector DNA into a sufficient quantity of SF9 insect cells 10 along with linearized baculovirus plasmid DNA by the calcium phosphate method or any other method generally known to those skilled in the art. (See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 15 (1987)). Recombinant viruses may be purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/ml) stocks of virus may be prepared.

Preferably, for large scale production, cells may be infected in approximately 10 liter fermentors (0.5×10^6 /ml) 20 with the recombinant virus stock such that the multiplicity of infection is greater than about 0.1. After several hours the cells are centrifuged and the cell pellet is homogenized in an appropriate buffer such as Tris/sucrose (50 mM/25%, pH 8.0). The homogenate may then be centrifuged at an 25 appropriate speed and for an appropriate time (such as $10,000 \times G$ for 30 minutes) so as to cause the homogenate to separate into a pellet and supernatant fraction. The resultant supernatant fraction will contain the desired product and may be stored at $-80^\circ C$ until use.

30 In order to test organic extracts for COX-2 inhibition and selectivity, standard COX-1 and COX-2 assays may be performed by employing ELISA procedures generally known to those skilled in the art. In such procedures, COX-1 and COX-2 activities are assayed as PGE_2 formed/ μg protein/time 35 using ELISA to detect the amount of PGE_2 synthesized from arachidonic acid. PGE_2 formation may be measured using PGE_2 specific antibody. Indomethacin, a non-selective COX-2/COX-

1 inhibitor, may be employed as a positive control. The
relative ability of various organic extracts to inhibit COX-
1 or COX-2 at a particular concentration may be determined
by comparing the IC_{50} value expressed as ug extract/ml
5 solvent resulting in a 50% inhibition of PGE2 production.
Selective inhibition of COX-2 may then be determined by the
 IC_{50} ratio of COX-1/COX-2. Additionally, any other means to
determine COX inhibition known to those generally skilled in
the art may be employed.

10 The extracts of this invention may be used to manage,
prevent and/or treat an organism having, or at risk for
developing, a condition which is mediated in whole or in
part by COX-2. Accordingly, conditions which may be
benefited by inhibition of COX-2 or selective inhibition of
15 COX-2 include, but are not limited to, the treatment of
inflammation in an organism, and for treatment of other
inflammation-associated disorders, such as, an analgesic in
the treatment of pain and headaches, or as an antipyretic
for the treatment of fever. For example, extracts of the
20 invention would be useful to treat arthritis, including but
not limited to rheumatoid arthritis, spondyloarthropathies,
gouty arthritis, osteoarthritis, systemic lupus
erythematosus and juvenile arthritis. Such extracts of the
invention would be useful in the treatment of asthma,
25 bronchitis, menstrual cramps, tendinitis, bursitis,
skin-related conditions such as psoriasis, eczema, burns and
dermatitis, and from post-operative inflammation including
ophthalmic surgery such as cataract surgery and refractive
surgery. Extracts of the invention also would be useful to
30 treat gastrointestinal conditions such as inflammatory bowel
disease, Crohn's disease, gastritis, irritable bowel
syndrome and ulcerative colitis, and treatment of cancer,
including but not limited to the following types of cancer:
colon, breast, prostate, bladder, or lung. In yet another
35 preferred use, the extracts of the present invention may
also be utilized as chemopreventive agents. Extracts of the
invention would be useful in treating inflammation in such

diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including

5 myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The extracts would also

10 be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The extracts would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic

15 fibrosis. Additionally, the extracts would be beneficial for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The extracts of the invention are useful as anti-inflammatory agents, such as for the treatment of

20 arthritis, with the additional benefit of having significantly less harmful side effects. These extracts would also be beneficial in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage

25 resulting from stroke, ischemia and trauma. Additionally, the extracts would be useful in the treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

The present extracts may also be employed either alone

30 or in combination with other compounds as a part of combination therapy, partially or completely, in place of other conventional anti-inflammatories. For example, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, leukotriene receptor antagonists, LTA4 hydrolase

35 inhibitors, and LTC4 synthase inhibitors. Preferably, with combination therapy one will typically combine a drug or drugs and a nutraceutical, such as a plant extract of the

current invention, in a manner such that the drug and the nutraceutical have different mechanisms of action, but yet target the same disease. For example, in a typical selection of agents for use in combination therapy to treat
5 arthritis, one could utilize a plant extract of the present invention, which exhibits selective COX-2 inhibition with another agent known to attenuate inflammation associated with arthritis via an independent mechanism.

Those of ordinary skill in the art of preparing
10 pharmaceutical formulations can readily formulate pharmaceutical compositions having plant extracts using known excipients (e.g., saline, glucose, starch, etc.). Similarly, those of ordinary skill in the art of preparing nutritional formulations can readily formulate nutritional
15 compositions having plant extracts. And those of ordinary skill in the art of preparing food or food ingredient formulations can readily formulate food compositions or food ingredient compositions having plant extracts.

In addition, those of ordinary skill in the art can
20 readily determine appropriate dosages that are necessary to achieve the desired therapeutic or prophylactic effect upon oral, parenteral, rectal and other administration forms. Typically, *in vivo* models (i.e., laboratory mammals) are used to determine the appropriate plasma concentrations
25 necessary to achieve a desired mitigation of inflammation related conditions.

The extracts of the present invention may be employed for the treatment and/or prevention of inflammation-related disorders, as identified above, in a number of organisms.
30 Besides being useful for human treatment, these extracts are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, cats, sheep, and pigs.

35 The detailed description set-forth above is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be

construed to unduly limit the present invention as
modifications and variation in the embodiments discussed
herein can be made by those of ordinary skill in the art
without departing from the spirit or scope of the present
5 inventive discovery.

All publications, patents, patent applications and
other references cited in this application are herein
incorporated by reference in their entirety as if each
individual publication, patent, patent application or other
10 reference were specifically and individually indicated to be
incorporated by reference.

Without further elaboration, it is believed that one
skilled in the art can, using the preceding description,
utilize the present invention to its fullest extent. The
15 following preferred specific embodiments are, therefore, to
be construed as merely illustrative, and not limitative of
the remainder of the disclosure in any way whatsoever.

Examples

Sample Preparation

20 Plants or parts thereof were dried and sliced
("sample"). Samples of organic extracts were prepared from
the plants listed in **Table 1**. The plant order and families
that the various samples were prepared from are set-forth in
Table 1. In addition, details regarding the use of these
25 some of these plants is set-forth in **Table 2**. The
particular sample was then ground into a fine powder using a
coffee grinder. Approximately 100 grams of the resulting
powder were added to approximately 500 ml of dichloromethane
and stirred at room temperature for about 1 hour. The
30 solvent was then removed by rotary evaporation, leaving
several grams of the particular extract.

Inhibitory Effect of Various Plant Organic Extracts on COX-1 and COX-2 Activity

The particular extracts resulting from the sample
35 preparation procedure detailed above were each evaluated for

inhibition of COX-1 and COX-2. The COX-1 and COX-2 inhibition activities were determined *in vitro* according to the method of Gierse et al., *J. Biochem.*, 305, 479-484 (1995). This method is summarized below.

5 Preparation of recombinant COX baculoviruses

Recombinant COX-1 was prepared by cloning a 2.0 kb fragment containing the coding region of human or murine COX-1 into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer
10 vectors for COX-1 according to the method of D.R. O'Reilly et al., *Baculovirus Expression Vectors: A Laboratory Manual* (1992).

Recombinant baculoviruses were then isolated by transfecting 4 ug of baculovirus transfer vector DNA into (2
15 $\times 10^8$) SF9 insect cells along with 200 ug of linearized baculovirus plasmid DNA by the calcium phosphate method. (See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987)). Recombinant
20 viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/ml) stocks of virus were prepared.

For large-scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6 /ml) with the
25 recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet was homogenized in Tris/sucrose (50 mM/25%, pH 8.0) containing 1% of 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS).
30 The homogenate was then centrifuged at $10,000 \times G$ for 30 minutes, and the resultant supernatant was stored at $-80^\circ C$ until use.

Recombinant COX-2 was prepared by cloning a 2.0 kb fragment containing the coding region of human or murine
35 COX-2 in accordance with the same method described above for COX-1.

Assay for COX-1 and COX-2 Activities

COX-1 and COX-2 activities were assayed as prostaglandin E2 (PGE2) formed/ug protein/time using ELISA to detect PGE2 synthesized from arachidonic acid. CHAPS-
5 solubilized insect cell membranes containing recombinant COX-1 or COX-2 enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme. Compounds were pre-incubated with the appropriate enzyme for approximately 10-20 minutes.
10 Arachidonic acid (10 uM) was then added to the mixture and the reaction was permitted to occur for ten minutes at room temperature (25° C).

Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes by transferring 40 ul
15 of reaction mixture into 160 ul ELISA buffer and 25 uM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, was utilized as a positive control. The PGE₂ formed was measured by standard ELISA technology utilizing a PGE2 specific antibody (Cayman Chemical).

20 Approximately 200 mg of each extract obtained from the sample preparation procedure set-forth above were each individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular extract. Potency was
25 determined by the IC₅₀ value expressed as ug extract/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 was determined by the IC₅₀ ratio of COX-1/COX-2. The results of these bioassays performed utilizing extract isolated from the plant family
30 indicated are reported in **Tables 1 and Figures 1-7** delineated below.

Table 1 below sets forth results of screening extracts of plants isolated from the orders, families, genera, and species indicated. A primary screen (indicated as 1° assay
35 in Table 1) was performed in order to determine particular extracts that inhibit COX-2 at a concentration of 10 ug/ml. The extracts were then subjected to a confirmation screen to

determine the extent of COX-2 inhibition at three different concentrations (10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). The extracts were then tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. The percentage of COX inhibition is indicated as a percentage in each column, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 was also determined for certain extracts as indicated in Table 1. The selectivity for these extracts was then determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above. The COX-2 selectivity of extracts whose IC_{50} value was not determined may be calculated by dividing the percentage of COX-1 inhibition (at a concentration of 10 ug/ml) by the percentage of COX-2 inhibition (at a concentration of 10 ug/ml).

Table 1: COX-2 Inhibitory Activity from Plant Extracts

Order	Family	Genus	Species	Common name	Part	1 st assay COX-2 (% inhib.) 10 ug/ml	Confirmation assay COX-2 (% inhib.) 10 ug/ml 3.3 ug/ml 1.1 ug/ml	COX-1 (% inhib.) 10 ug/ml	IC50 (ug/ml) COX-2	IC50 (ug/ml) COX-1	Selectivity COX-2/COX-1
Agavales	Agavaceae	Pleomele	augustifolia	native dracaena	LF	63%	73% 23% 22%	40%	***	***	***
Apocynales	Apocynaceae	Bleekeria	vitensis			**	58% 34% -16%	***	***	***	***
Apocynales	Apocynaceae	Strophanthus	hispidus	zwezwe (Africa)	LP	69%	72% 22% -1%	6%	***	***	***
Apocynales	Asclepiadaceae	Asclepias	asperula	antelope horn	RT	68%	70% 50% 24%	1%	***	***	***
Arales ⁹	Araceae	Amorphophallus	campanulatus	telinga potato	CO	70%	58% 27% 2%	-3%	***	***	***
Arales ⁹	Araceae	Anthurium	crenatum		PX	65%	65% 3% 1%	23%	***	***	***
Arales ⁹	Araceae	Pinellia	ternata	ban xia (China)		*	64% 18% 2%	***	***	***	***
Arales ⁹	Araceae	Pinellia	ternata	ban xia (China)		*	98% 72% 38%	28%	***	***	***
Asterales	Asteraceae	Vernonia	sericea		PX	77%	77% 30% 19%	12%	***	***	***
Asterales	Asteraceae	Wedelia	reticulata		PX	77%	63% 37% 1%	17%	***	***	***
Asterales	Asteraceae	Xanthium	strumarium	arishia (Sanskrit)	FR	99%	75% 62% 39%	37%	***	***	***
Basidiomycetae	Polyporaceae	Grifola	frondosa	maitake	FB	67%	68% 26% -2%	17%	***	***	***
Brassicales ¹	Brassicaceae ²	Brassica	chinensis	Chinese cabbage		50%	68% 38% -5%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Brassica	chinensis	Chinese cabbage		61%	22% 16% -14%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Brassica	oleracea	common cabbage		*	41% 31% 15%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Brassica	oleracea	common cabbage		*	74% 38% 6%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Raphanus	sativus	daikon; semen raphani		76%	81% 56% 5%	25%	***	***	***
Brassicales ¹	Brassicaceae ²	Raphanus	sativus	daikon; semen raphani		71%	29% 18% -10%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Raphanus	sativus	daikon; semen raphani		*	42% 34% 6%	***	***	***	***
Brassicales ¹	Brassicaceae ²	Raphanus	sativus	daikon; semen raphani		*	54% 19% 10%	***	***	***	***
Caryophyllales	Caryophyllaceae	Saponaria	officinalis	soapwort		*	30% 13% 6%	***	***	***	***
Caryophyllales	Caryophyllaceae	Saponaria	officinalis	soapwort		*	42% -4%	***	***	***	***
Caryophyllales	Cenopodiaceae	Beta	vulgaris	beet; Swiss chard	RT	85%	75% 48% 35%	37%	***	***	***
Caryophyllales	Nyctaginaceae	Pisonia	aculeata	cockspur; una de gato	LP	61%	97% 63% 47%	6%	4.5	45	10
Caryophyllales	Phytolaccaceae	Trichostigma	octandrum	hoop vine	PX	73%	82% 40% 33%	43%	***	***	***
Caryophyllales	Polygonaceae	Chorizanthe	diffusa			62%	46% 31% -14%	***	***	***	***
Caryophyllales	Polygonaceae	Rumex	hymenosepalus	Indian root; wild rhubarb		*	58% 12% 5%	***	***	***	***
Caryophyllales	Polygonaceae	Rumex	hymenosepalus	Indian root; wild rhubarb		*	83% 67% 34%	36%	***	***	***
Cycadales	Cycadaceae	Zamia	debilis	wild sago		30%	66% 29% -4%	***	***	***	***
Cycadales	Cycadaceae	Zamia	debilis	wild sago		66%	2% -11%	***	***	***	***
Ebenales	Ebenaceae	Diospyros	unidentified	persimmon	LF	85%	75% 53% 31%	10%	***	***	***
Euphorbiales	Euphorbiaceae	Croton	rigidus		PX	69%	79% 61% 21%	47%	***	***	***
Euphorbiales	Euphorbiaceae	Gymnanthes	lucida		PX	63%	79% 61% 9%	53%	***	***	***
Euphorbiales	Euphorbiaceae	Macaranga	confira		LF	66%	64% 25% 13%	36%	***	***	***
Euphorbiales	Euphorbiaceae	Macaranga	triloba		LF	62%	57% 32% 48%	29%	***	***	***
Euphorbiales	Euphorbiaceae	Manihot	esculenta	mahang serindit (Malaysia)	RB	71%	69% 40% 21%	25%	***	***	***
Euphorbiales	Euphorbiaceae	Ostodes	paniculata	cassava		*	48% 11% -1%	***	***	***	***
Euphorbiales	Euphorbiaceae	Ostodes	paniculata	bijopari		*	41% 15% -18%	***	***	***	***
Euphorbiales	Euphorbiaceae	Phyllanthus	cuneifolius		PX	64%	62% 25% 1%	46%	***	***	***
Euphorbiales	Euphorbiaceae	Ricinodendron	heudelottii		ST	73%	82% 65% 32%	55%	***	***	***
Fagales	Fagaceae	Castanopsis	unidentified		LF	86%	64% 23% -1%	41%	***	***	***
Fagales	Fagaceae	Castanopsis	unidentified		LF	73%	56% 15% 15%	30%	***	***	***
Fagales	Fagaceae	Castanopsis	unidentified		LF	66%	60% 36% 4%	21%	***	***	***

Table 1: COX-2 Inhibitory Activity from Plant Extracts

Order	Family	Genus	Species	Common name	Part	1° assay COX-2 (% inh.) 10 ug/ml	Confirmation assay COX-2 (% inh.) 10 ug/ml 3.3 ug/ml 1.1 ug/ml	COX-1 (% inh.) 10 ug/ml	IC50 (ug/ml) COX-2	IC50 (ug/ml) COX-1	Selectivity COX-2/COX-1
Hydrocharitales	Hydrocharitaceae	Elodea	densa	water weed		100%	90% 78% 30%	***	***	***	***
Lamiales	Verbenaceae	Callacarpa	cana		SB	66%	71% 56% 11%	45%	***	***	***
Lamiales	Verbenaceae	Clerodendron	lecomtei		LF	60%	80% 54% 31%	23%	***	***	***
Liliales	Commelinaceae	Tradescantia	virginiana	spiderwort		**	96% 56% 25%	13%	2.5	75	30
Liliales	Commelinaceae	Tradescantia	virginiana	spiderwort		**	67% 48% -3%	***	***	***	***
Liliales	Liliaceae	Lilium	auratum	goldband lilly	R4	73%	78% 47% 31%	34%	***	***	***
Liliales	Liliaceae	Lilium	auratum	goldband lilly	BU	73%	70% 61% 25%	40%	***	***	***
Liliales	Liliaceae	Lilium	auratum	goldband lilly		*	75% 49% 30%	16%	***	***	***
Liliales	Liliaceae	Smilax	havanensis	Cuban sarsaparilla	PX	60%	80% -4% 21%	15%	***	***	***
Loasales	Loasaceae	Mentzelia	aspera	dal pega	PX	79%	77% 46% 17%	35%	***	***	***
Malvales	Bombaceae ⁸	Quararibea	turbinata	swizzle stick tree	PX	60%	47% 12%	19%	***	***	***
Malvales	Elaeocarpaceae	Elaeocarpus	bifidus			62%	85% 62% 1%	12%	***	***	***
Malvales	Elaeocarpaceae	Elaeocarpus	bifidus			52%	37% 54% -13%	***	***	***	***
Malvales	Sterculiaceae	Guazuma	ulmifolia	bay cedar	PX	77%	71% 40% -6%	17%	***	***	***
Malvales	Sterculiaceae	Helicteres	jamaicensis	Jamaican screw tree	PX	63%	66% 32% 33%	23%	***	***	***
Malvales	Sterculiaceae	Melochia	pyramidata	meloch	PX	66%	61% 14% -9%	-44%	***	***	***
Myrtales	Myrtaceae	Myrcia	splendens		PX	61%	72% 30% 23%	3%	***	***	***
Myrtales	Myrtaceae	Syzygium	malaccense	Malay apple	PX	65%	62% 15%	-7%	***	***	***
No order	Cyatheaceae	Cyathea	unidentified	fern	PE	73%	100% 22%	-13%	***	***	***
No order	Umbelliferae	Umbellifera	probovidea	umbilicaria lichen	PL	76%	81% 25%	61%	***	***	***
No order	Boletaceae	Boletus	rubricitrinus			87%	70% 59% 35%	34%	***	***	***
Palmales	Areaceae	Caryota	mitis	sago palm	BK	61%	92% 62%	37%	***	***	***
Palmales	Areaceae	Coccothrinax	alta	chestnut; silver palm	PX	76%	73% 35%	2%	***	***	***
Palmales	Areaceae	Scheelea	phalerata	scheelea palm	LQ	67%	76% 22%	42%	***	***	***
Pandanales ⁹	Sparganiaceae	Sparganium	ramosum	bur-reed		*	58% 42%	25%	***	***	***
Papaverales	Papaveraceae	Bocconia	frutescens	tree celandine	PX	71%	78% 40%	39%	***	***	***
Piperiales	Chloranthaceae	Hedyosmum	arborescens		PX	73%	54% 25%	4%	***	***	***
Piperiales	Piperaceae	Peperomia	unidentified	pepper	PL	95%	66% 28%	90%	***	***	***
Piperiales	Piperaceae	Piper	aduncum	pepper	PL	72%	83% 23%	34%	***	***	***
Polemoniales ⁷	Boraginaceae ⁶	Cordia	laevigata		PX	66%	74% 42%	19%	***	***	***
Polemoniales ⁷	Boraginaceae ⁶	Lithospermum	erythrorhizon	red root gromwell	RT	61%	31% 18%	-21%	***	***	***
Polemoniales ⁷	Solanaceae	Capsicum	frutescens	habanero pepper	FR	60%	81% 50%	4%	2.5	>100	>40
Polemoniales ⁷	Solanaceae	Capsicum	frutescens	habanero pepper		*	59% 11%	4%	***	***	***
Polemoniales ⁷	Solanaceae	Capsicum	frutescens	habanero pepper		*	82% 64%	40%	30%	***	***
Polemoniales ⁷	Solanaceae	Solanum	acuminatum		KS	76%	81% 39%	27%	***	***	***
Polygalales	Polygalaceae	Polygala	penaca		PX	71%	72% 28%	8%	***	***	***
Primulales	Myrsinaceae	Myrsine	coriacea		PX	78%	83% 58%	18%	***	***	***
Primulales	Theophrastiaceae	Jacquinia	umbellata		PX	79%	79% 37%	19%	***	***	***
Primulales	Theophrastiaceae	Jacquinia	umbellata		PX	75%	78% 42%	-2%	***	***	***
Ranales	Lauraceae	Cinnamomum	obtusifolium	cinnamon	LF	65%	65% -22%	-1%	***	***	***
Ranales	Lauraceae	Cinnamomum	parthenoxylon	cinnamon	LF	79%	52% 6%	6%	***	***	***
Ranales	Ranunculaceae	Paeonia	officinalis	common peony		45%	51% 15%	-17%	***	***	***
Rhamnales	Ziziphaceae	Ziziphus	jujuba	jujube; date tree	SD	76%	69% 61%	41%	***	***	***
Rhamnales	Rhamnaceae	Ziziphus	jujuba	jujube; date tree		*	86% 72%	53%	***	***	***

Table 1: COX-2 Inhibitory Activity from Plant Extracts

Order	Family	Genus	Species	Common name	Part	i ^o assay COX-2 (% inhib.) 10 µg/ml	Confirmation assay COX-2 (% inhib.) 10 µg/ml 3.3 µg/ml 1.1 µg/ml	COX-1 (% inhib.) 10 µg/ml	IC50 (µg/ml) COX-2	IC50 (µg/ml) COX-1	Selectivity COX-2/COX-1
Rhamnales	Rhamnaceae	Ziziphus	jujuba	jujube; date tree		*	88% 74% 42%	31%	***	***	***
Rosales	Fabaceae	Adenanthera	microsperma	bead tree	LF	67%	58% 29% 21%	41%	***	***	***
Rosales	Fabaceae	Albizia	lucida		LF	81%	62% 26% 29%	13%	***	***	***
Rosales	Fabaceae	Albizia	longepedata			68%	-3% 14% -14%	***	***	***	***
Rosales	Fabaceae	Cassia	quinquangulata	wampi		28%	57% 34% 2%	***	***	***	***
Rosales	Fabaceae	Erythrina	rubrinervia	culantro; galito		68%	71% 18% -32%	***	***	***	***
Rosales	Fabaceae	Erythrina	rubrinervia	culantro; galito		100%	75% 36% -10%	18%	4	45	11
Rosales	Fabaceae	Erythrina	rubrinervia	culantro; galito		50%	48% 13% -43%	***	***	***	***
Rosales	Fabaceae	Erythrina	rubrinervia	culantro; galito		75%	61% 42% -20%	***	***	***	***
Rosales	Fabaceae	Inga	edulis	guavo; ice cream bean	AR	84%	82% 57% 31%	34%	***	***	***
Rosales	Fabaceae	Milletia	unidentified		LF	61%	81% 42% 25%	46%	***	***	***
Rosales	Fabaceae	Tephrosia	purpurea	purple tephrosia		60%	68% 32% -9%	***	***	***	***
Rosales	Fabaceae	Tephrosia	purpurea	purple tephrosia		98%	71% 46% 8%	7%	4	>100	>25
Rosales	Rosaceae	Eriobotrya	unidentified		LF	80%	55% 15% 10%	34%	***	***	***
Rubiales	Saxifragaceae	Mitella	japonica	tyraumeruso		*	60% 28% 22%	***	***	***	***
Rubiales	Rubiaceae	Berberia	ocymoides		LF	79%	72% 36% 10%	39%	***	***	***
Rubiales	Rubiaceae	Genipa	americana	genip	FR	73%	63% 31% 32%	28%	***	***	***
Rubiales	Rubiaceae	Hamelia	axillaris	yutobanco (Peru)	PX	75%	68% 14% 2%	32%	***	***	***
Rubiales	Rubiaceae	Hamelia	axillaris	yutobanco (Peru)	PX	61%	68% 38% 10%	-4%	***	***	***
Rubiales	Rubiaceae	Nauclea	orientalis	mau (Burma)	FU	84%	57% 17% -16%	44%	***	***	***
Rubiales	Rubiaceae	Psychotria	microdon	tapa camino	PX	74%	83% 48% 11%	30%	***	***	***
Rubiales	Rubiaceae	Psychotria	pubescens	chak k'anan	PX	74%	68% 44% 31%	13%	***	***	***
Rubiales	Rubiaceae	Psychotria	uliginosa	tres cabezas (Mexico)	PX	69%	88% 70% 46%	63%	***	***	***
Rubiales	Rubiaceae	Psychotria	unidentified		BK	95%	81% 66% 51%	79%	***	***	***
Rutales ¹	Meliaceae	Dysoxylum	excelsum		LF	85%	76% 27% 0%	48%	***	***	***
Rutales ¹	Meliaceae	Scindapsus	pictus		PL	76%	70% 28% 5%	23%	***	***	***
Rutales ¹	Meliaceae	Trichilia	hirta	broom wood		80%	90% 61% 20%	38%	***	***	***
Rutales ¹	Meliaceae	Trichilia	hirta	broom wood		98%	78% 57% 3%	17%	1.5	75	50
Rutales ¹	Rutaceae	Clausena	lansium	Chinese wampee	SB	96%	85% 68% 43%	44%	***	***	***
Rutales ¹	Rutaceae	Clausena	lansium	Chinese wampee	LF	72%	70% 47% 27%	40%	***	***	***
Rutales ¹	Rutaceae	Zanthoxylum	fagara	wild lime		*	40% 6% 2%	***	***	***	***
Rutales ¹	Rutaceae	Zanthoxylum	fagara	wild lime		*	57% 24% 6%	***	***	***	***
Rutales ¹	Rutaceae	Zanthoxylum	piperitum	Japanese pepper		**	64% 42% -20%	***	***	***	***
Rutales ¹	Simaroubaceae	Brucea	javanica	kosam seed; java brucea	SD	66%	51% 27% 16%	16%	***	***	***
Rutales ¹	Simaroubaceae	Picramnia	pentandra	bitter bush	PX	64%	55% 10% -1%	14%	***	***	***
Santalales	Loranthaceae	Phoradendron	piperoid	pajar (Peru)	PX	69%	75% 43% 18%	9%	***	***	***
Sapindales ¹	Anacardiaceae	Dracontomelon	dao	argus pheasant tree	FR	60%	74% 53% 13%	3%	***	***	***
Sapindales ¹	Anacardiaceae	Dracontomelon	mangiferum	sengkuang		56%	79% 47% 12%	3%	1.8	38	21
Sapindales ¹	Anacardiaceae	Dracontomelon	unidentified			76%	86% 60% 32%	2%	3.5	80	23
Sapindales ¹	Anacardiaceae	Dracontomelon	unidentified			59%	40% -5% -22%	***	***	***	***
Sapindales ¹	Icacinaceae	Pyrenacantha	staudtii	abere (Nigeria)		**	73% 50% 11%	***	***	***	***
Scrophulariales	Bignoniaceae	Macfadyena	unguis-cati	cat's claw	PX	83%	69% 40% 17%	29%	***	***	***

Table 1: COX-2 Inhibitory Activity from Plant Extracts

Order	Family	Genus	Species	Common name	Part	1° assay COX-2 (% inhib.) 10 ug/ml	Confirmation assay COX-2 (% inhib.) 10 ug/ml 3.3 ug/ml 1.1 ug/ml	COX-1 (% inhib.) 10 ug/ml	IC50 (ug/ml) COX-2	IC50 (ug/ml) COX-1	Selectivity COX-2/COX-1
Scrophulariales	Gesneriaceae	Cyrtandra	grandis		PL	74%	54% 18% 10%	24%	***	***	***
Umbellales	Apiaceae ¹	Apium	graviolens	celery seed	SD	72%	68% 51% 25%	30%	***	***	***
Umbellales	Araliaceae	Arthophyllum	diversifolium		LF	70%	74% 36% -14%	30%	***	***	***
Umbellales	Araliaceae	Arthophyllum	diversifolium		PE	69%	65% 32% -15%	12%	***	***	***
Umbellales	Araliaceae	Arthophyllum	diversifolium		SB	63%	49% -3% -19%	8%	***	***	***
Umbellales	Araliaceae	Brassatopsis	glomerata		LF	69%	66% 37% -8%	52%	***	***	***
Urticales	Moraceae	Dorstenia	contrajerva	contrayerba	PX	61%	69% 23% 15%	0%	***	***	***
Urticales	Moraceae	Ficus	ribes	fig	LF	61%	61% 34% 20%	12%	***	***	***
Urticales	Moraceae	Streblus	unidentified		LF	88%	61% 43% 27%	48%	***	***	***
Urticales	Ulmaceae	Celtis	unidentified		LF	60%	62% 19% 16%	13%	***	***	***
Violales	Flacourtiaceae	Pangium	edule	kluwak; pakem	LF	96%	92% 59% 45%	71%	***	***	***
Violales	Flacourtiaceae	Pangium	edule	kluwak; pakem	FR	80%	75% 66% 55%	82%	***	***	***
Violales	Flacourtiaceae	Pangium	edule	kluwak; pakem	BK	77%	72% 28% 31%	44%	***	***	***
Violales	Flacourtiaceae	Ryparosa	caesia		TW	77%	69% 31% -10%	23%	***	***	***
Violales	Flacourtiaceae	Ryparosa	caesia		LF	67%	59% 20% -6%	35%	***	***	***

* Primary screen performed at three concentrations. Samples were not repeated in a COX-2 confirmation assay.

** No data due to assay error.

*** Not tested.

¹Brassicaceae also classified as Sapindales or Rutales

²Brassicaceae also classified as Cruciferae

³Apiaceae also classified as Umbelliferae

⁴Boraginaceae also classified as Cordiaceae or Ehretiaceae

⁵Polemoniaceae also classified as Solanaceae

⁶Bombacaceae also classified as Bombacaceae

⁷Pandanaceae also classified as Arales or Alismatales

The order, family, genus, and species of each plant extract are indicated.

As illustrated by the data in Table 1, the organic extracts isolated from the indicated plant orders inhibit
5 COX-2. In fact, several of the extracts selectively inhibit COX-2 over COX-1 by greater than 10 fold.

Table 2 below provides a description detailing the particular use of some of the plant extracts tested for COX-2 inhibition as set-forth in **Table 1**. In addition, a
10 comprehensive listing of references known to those generally skilled in the art is provided.

Table 2 -USES OF PLANT EXTRACTS

Scientific Name	Common Name	Isolate / Chemical ID	Sample ID	Extract #	Reference
15 Adenanthera microsperma	bead tree			P-01683	5
Medicinal					
Albizzia lucida	No common name avail.			P-01679	
Seeds are oily and edible.					
20 Albizzia longepedata	Species not found.	81259	935226		
Other species edible.					
Amorphophallus campanulatus	telinga potato			P-00723	3
Leaves and tubers are eaten.					
25 Apium graveolens	celery			P-01897	1, 2, 3, 4

- 5 Leaves and leafstalks are used in salad, for flavoring soups, or as vegetable. The seed is the source of celery, containing d-limonene, sefinene and sesquiterpene, used in culinary sauces or for manufacturing celery salt.

Asclepias	Antelope			P-00264	5
asperula	horns				

Medicinal

Beta vulgaris	beet or			P-01120	1,2,3,
	Swiss				4
	chard				

- 10 Roots are consumed as vegetable when cooked, in salads. Leaves are sometimes eaten as potherb.

Bleekeria	No common	81255	9351		5
vitiensis	name		85		
	available.				

Medicinal

- 15 **Bocconia** Ree
frutescens celandine

P-02163 6

Medicinal

Boletus	Species			P-01876	
rubricitrinus	not found.				

- 20 Fruiting bodies of some species of this mushroom are edible.

Brassica	Chinese	81272	9352		1,2,3,
chinensis	cabbage		02		4

Eaten like lettuce.

- 25 **Brassica oleracea** common
cabbage

81437 9369
37

1,2,3

Eaten raw or cooked.

Brucea javanica	kosam			P-00090	5
	seed; Java				
	brucea				

Medicinal					
Callicarpa cana		No common name		P-01942	5
Berries sometimes eaten.					
5	Capsicum frutescens	habanero pepper	81442	93699 7	1,2,3, 4
Fruits are edible, eaten as vegetable or used as condiment.					
Caryota mitis		sago palm		P-01601	2
Buds and seeds are edible.					
10	Cassia quinquangulata	wampi	81274	93520 4	5
Medicinal					
Castanopsis unidentified				P-01955	
15	Fruits of most species edible.				
Celtis unidentified				P-01958	
Species not found, but fruits of some species are edible.					
20	Chorizanthe diffusa		81260	93522 7	5
Ornamental; not edible					
Cinnamomum obtusifolium				P-01961	
25	Species not found. Genus of true cinnamons. Edible as condiment.				
Cinnamomum parthenoxylon				P-01964	
30	Species not found. Genus of true cinnamons. Edible as condiment.				
Clausena lansium		Chinese wampee		P-01967	1,2,3

The fruit is eaten fresh, preserved, made into jam, pies, or refreshing drinks. Leaves are put into curries.

5	Clerodendron				P-01969	5
	lecomtei					

Species not found, but others are medicinal.

	Coccothrinax alta	silver			P-02204	5
		palm				

Buds and seeds are edible

	Cordia laevigata	Species			P-02102	
		not found.				

The fruits of many species are edible.

	Croton rigidus				P-02092	5
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Species not found but most other Crotons are poisonous or medicinal.

15	Cyathea				P-01256	
	unidentified					

Other species of this fern used to make a starch.

	Cyrtandra grandis				P-01741	
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Species not found. Leaves of several other species used as flavorings or chewed like betel.

20	Diospyros				P-01606	
	unidentified					

Genus of persimmons. Fruits of many species edible.

	Dorstenia	contrayer			P-02213	6
	contrajerva	ba				

Medicinal

25	Dracontomelon dao	argus			P-02250	3
		pheasant				
		tree				

Fruits are edible, usually mixed with soy sauce in rice.

	Dracontomelon mangiferum	sengkuang	81282	93521 2		5
	Fruits are edible, usually mixed with soy sauce in rice.					
5	Dracontomelon unidentified (Draconotomelum)		81283	93521 3		
	Fruits of most species edible.					
10	Dysoxylum excelsum				P-01743	5
	Species not found, but others are medicinal.					
	Elaeocarpus bifidus	No common name.	81268	93523 5		5
	Fruits edible.					
15	Elodea densa	water weed genus	81278	93524 5		5
	Medicinal					
	Eriobotrya unidentified				P-01670	
	Species not found. <i>Eriobotrya japonica</i> fruit edible.					
20	Erythrina rubrinervia	culantro	81252	93518 2		3
	Flowers and flower buds eaten cooked like string beans in El Salvador and Guatemala. Leaves eaten in soups.					
25	Ficus ribes	fig genus			P-01736	2
	Medicinal					
	Genipa americana	genip			P-01810	3
	Fruits are edible when soft and overripe.					
	Grifola frondosa	maitake			P-00001	1,2,3
30	Fruit bodies are edible.					

Guazuma ulmifolia	bay cedar			P-02234	3
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Green fruits are eaten raw, cooked, crushed in water to make a beverage, or used to flavor other foods.

Gymnanthes lucida	No common name available			P-02183	5
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Medicinal

Hamelia axillaries	yutobanco (Peru)			P-02210	5
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Medicinal

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Hedyosmum arborescens	sago palm; species not found			P-02238	
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At least on other species (*mexicana*) has edible fruits and leaves may be used as tea.

Helicteres jamaicensis	Jamaican screw tree			P-02142	5
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15

Medicinal

Inga edulis	guavo, ice cream bean			P-02780	1, 5
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Pulp of the fruit is eaten.

Jacquinia umbellata	Species not found.			P-02137	5
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Other species are fish poisons or insecticides.

Lilium auratum	goldband lily	81431	93698 6		3
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Mucilaginous bulb is eaten boiled, sweetened, powdered and added to dumplings.

Lithospermum	red root			P-00002	5
erythrorhizon	gromwell				

Medicinal

5	Macaranga	Species			P-01168	5
	conifera	not found.				

Medicinal

	Macaranga triloba	Mahang serndit (Malaya)			P-01128	5
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Medicinal

10	Macfadyena	cat's			P-02215	5
	unguis-cati	claw				

Medicinal

	Manihot esculenta	cassava			P-00204	1,2,3, 4
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Young leaves and stems are eaten steamed. Tubers are eaten cooked or fried. They are ground into flour.

15	Melochia	meloch			P-02127	5
	pyramidata					

Fruit fermented as a beverage.

	Mentzelia aspera	dal pega			P-02126	5
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Medicinal

20	Milletia				P02035	5
	unidentified					

Most species used as insecticides, fish poisons and medicinals.

	Mitella japonica	tyraumeru	81439	93699		5
		so		4		

25						
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Medicinal

	Myrcia splendens				P-02236	5
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Medicinal					
Myrsine coriaceae					
Species not found. Fruit of other species edible.					
5	Nauclea	mau		P-01239	3
	orientalis	(Burmese)			
Young leaves and tender tips are steamed and eaten with rice.					
10	Ostodes	bijopari	81445	93697	5
	paniculata			5	
Medicinal					
15	Paeonia	common	81266	93519	3
	officinalis	peony		6	
Hot seeds were ground into a spice in Europe. Mongolians mad a tea from them. Flowers are eaten as a vegetable or used to scent tea.					
20	Pangium edule	pakem		P-02986	2
	Seeds are edible.				
25	Peperomia			P-02465	5
	unidentified				
Most species are medicinal.					
30	Phoradendron	pajar		P-02205	5
	piperoid	(Peru)			
Medicinal					
30	Phyllanthus	Species		P-02144	5
	cuneifolius	not found.			
Medicinal					
30	Picramnia	bitter		P-02214	5
	pentandra	bush			
Medicinal					
30	Pinellia ternata	ban xia	81434	93698	2
		(Chinese)		9	

Subterranean tubers are edible.

Piper aduncum	pepper			P-02466	3
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Peppery fruits used to season foods. Very sweet when black and ripe. Leaves eaten as potherb.

Pisonia aculeate	cockspur			P-01806	5
	; una de				
	gato				

Medicinal

Pleomele	native			P-02692	2
angustifolia	dracaena				

Young leaves are eaten cooked. Sometimes used to add green color to foodstuff.

Psychotria	tapa			P-02099	5
microdon	camino				

Medicinal

Psychotria	chak k'		P-02212	5
pubescens	anan			

Medicinal

Psychotria	tres			P-02077	5
uliginosa	cabezas				
	(Mexico)				

Medicinal

Psychotria				P-01592	5
unidentified					

Most species are medicinal

Pyrenacantha	abere	81271	93520		5
staudtii	(Nigeria)		1		

Medicinal

Quararibea	swizzle			P-02190	2,
turbinata	stick				3,5
	tree				

Year	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1970	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100

Twigs used in mixing beverages. Fruit may be edible.

Raphanus sativus	daikon, se men raphani	81438	93699 3		1,2,3, 4
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Fresh roots are eaten as salad or appetizer,
occasionally cooked. Leaves are eaten as greens.

5 Inflorescences are similarly eaten.

Ricinodendron heudelottii				P-00183	2
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Probably *Ricinodendron heudelottii* var. *africanum*.
Seeds are edible.

10 Rumex hymenosepalus	Indian root, wild rhubarb	81450	93700 5	937005	3
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Leafstalks eaten like rhubarb. Leaves eaten after
wash to remove tannins. Seeds are edible.

Ryparosa caesia	No common name available			P-01756	2
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15 Fruit is edible.

Saponaria officinalis	soapwort	81451	93700 6		3
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An extract of the roots used as an emulsifying agent
in foods. The flowers are occasionally added to salads.

20 Scheelea phalerata	scheela palm			P-02777	
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Oil used in cooking

Smilax havanensis	Cuban sarsapari lla			P-02128	5
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Medicinal

25 Solanum acuminatum				P-02461	5
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Species not found. This is the genus of nightshades, so most are either medicinal or poisonous.

Sparganium	bur-reed	81433	93698		2
ramosum			8		

- 5 Young stems are peeled and boiled down for food.

Streblus				P-01665	
unidentified					

Milk from stem of *Streblus asper* is used to curdle milk. Fruit is edible.

- 10 **Strophanthus** zwezwe
hispidus (African)

P-00294 5

Medicinal

Syzygium	Malay			P-02201	3
malaccense	apple				

- 15 Used with seeds to make beverage.

Tephrosia	purple	81267	93523		1,2,3,
purpurea	tephrosia		4		4

Seeds used as a substitute for coffee. Roots are used as a flavoring for milk.

- 20 **Tradescantia** spiderwor
virginiana t

81279 93524
6 3

Very young shoots and leaves eaten in salads. Flowers are an edible garnish.

Trichilia hirta	broom	81264	93519		5
	wood		4		

- 25 Species not found, but others are medicinal.

Trichostigma	hoop vine			P-02162	
octandrum					

Medicinal

- 30 **Umbilicaria** umbilicar
proboscidea ia lichen

P-02749 5

An edible lichen.

Veronina sericea	Species not found.			P-02110	5
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Medicinal

Wedelia reticulata	Species not found.			P-02209	5
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Medicinal

5 Xanthium strumarium	arishta (Sanskrit)			P-01830	2
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10 Young shoots are eaten cooked, as are young plants. Seeds are ground into flour and made into noodle. Fruit is sun-dried, roasted and put into dumplings or cooked with rice.

Zamia debilis	wild sago	81261	93522		5
			8		

Tubers are source for starch.

Zanthoxylum fagara	wild lime	81429	93695		5
			9		

15 Medicinal

Zanthoxylum piperitum	Japanese pepper	81247	93517		1,2,3
			7		

20 Young leaves and fruit are used in dishes; the former being used in Japanese soups, the latter is cooked into tsukudani. Bark is also employed for seasoning.

Ziziphus jujuba	jujube; date tree	81435	93696	936965	3
			5		

Fruits are edible.

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Tables 3-9 further illustrate the ability of certain extracts isolated from the families identified in Table 1 to selectively inhibit COX-2. A total of six different concentrations of the various extracts were tested for their ability to inhibit both COX-1 and COX-2. The IC₅₀ value for COX-1 and COX-2 was also determined and a selectivity ratio was then calculated as set forth above. **Figures 1-7** are graphs that depict the data shown in **Tables 3-9** as indicated.

Table 3 - Extract isolated from *Trichilia hirta*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	46%	Not determined
33.3	63%	11%
11.1	79%	16%
3.70	102%	30%
1.23	112%	53%
0.41	135%	81%

IC ₅₀ (ug/ml) COX-1	IC ₅₀ (ug/ml) COX-2	COX-2 Selectivity Ratio
75	1.5	50

Table 4 - Extract isolated from *Capsicum frutescens*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	53%	Not determined
33.3	116%	12%
11.1	152%	17%
3.70	140%	42%
1.23	132%	63%
0.41	182%	104%

IC ₅₀ (ug/ml)	IC ₅₀ (ug/ml)	COX-2 Selectivity Ratio
COX-1	COX-2	
>100	2.5	>40

Table 5 - Extract isolated from *Tradescantia virginiana*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	37%	Not determined
33.3	89%	Not determined
11.1	124%	16%
3.70	112%	44%
1.23	113%	61%
0.41	144%	83%

IC ₅₀	IC ₅₀	COX-2
(ug/ml)	(ug/ml)	Selectivity
COX-1	COX-2	Ratio
75	2.5	30

5 **Table 6 - Extract isolated from *Tephrosia purpurea***

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	80%	Not determined
33.3	92%	Not determined
11.1	95%	18%
3.70	106%	52%
1.23	102%	67%
0.41	133%	92%

15

IC ₅₀	IC ₅₀	COX-2
(ug/ml)	(ug/ml)	Selectivity
COX-1	COX-2	Ratio
>100	4	>25

20 **Table 7 - Extract isolated from *Dracontomelon mangiferum***

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	25%	Not determined
33.3	53%	Not determined
11.1	91%	16%

25

3.70	117%	39%
1.23	114%	55%
0.41	141%	81%

5

IC ₅₀ (ug/ml)	IC ₅₀ (ug/ml)	COX-2 Selectivity
COX-1	COX-2	Ratio
38	1.8	21

Table 8 - Extract isolated from *Erythrina rubrinervia*

10

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	31%	Not determined
33.3	57%	Not determined
11.1	76%	16%
3.70	106%	51%
1.23	109%	72%
0.41	139%	73%

15

20

IC ₅₀ (ug/ml)	IC ₅₀ (ug/ml)	COX-2 Selectivity
COX-1	COX-2	Ratio
45	4	11

Table 9 - Extract isolated from *Pisonia aculeata*

25

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
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100	26%	Not determined
33.3	60%	10%
11.1	119%	27%
3.70	140%	56%
1.23	122%	71%
0.41	160%	87%

10

IC ₅₀ (ug/ml)	IC ₅₀ (ug/ml)	COX-2 Selectivity
COX-1	COX-2	Ratio
45	4.5	10

As illustrated by these data, the organic extracts isolated from the indicated plants inhibit COX-2. In fact, all of the extracts selectively inhibit COX-2 over COX-1 by greater than or equal to 10-fold. In view of the above, it will be seen that the several objectives of the invention are achieved and other advantageous results attained.